



PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Article 36 and Rule 70)

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| Applicant's or agent's file reference JAB1721f-PCT | | FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEA/416) | |
| International application No. PCT/EP 03/50374 | International filing date (day/month/year) 12.08.2003 | Priority date (day/month/year) 12.08.2002 | |
| International Patent Classification (IPC) or both national classification and IPC C07D498/04 | | | |
| Applicant JANSSEN PHARMACEUTICA N.V. | | | |
| <p>1. This International preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 5 sheets, including this cover sheet.</p> <p><input type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of sheets.</p> | | | |
| <p>3. This report contains indications relating to the following items:</p> <p>I <input checked="" type="checkbox"/> Basis of the opinion</p> <p>II <input type="checkbox"/> Priority</p> <p>III <input checked="" type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p>IV <input type="checkbox"/> Lack of unity of invention</p> <p>V <input checked="" type="checkbox"/> Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p>VI <input type="checkbox"/> Certain documents cited</p> <p>VII <input type="checkbox"/> Certain defects in the international application</p> <p>VIII <input type="checkbox"/> Certain observations on the international application</p> | | | |
| Date of submission of the demand 24.01.2004 | | Date of completion of this report 14.07.2004 | |
| Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465 | | Authorized Officer Härtinger, S Telephone No. +49 89 2399-8289  | |

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No.

PCT/EP 03/50374

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*):

Description, Pages

1-46 as originally filed

Claims, Numbers

1-16 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
☐ the language of publication of the international application (under Rule 48.3(b)).
☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority in written form.
☐ furnished subsequently to this Authority in computer readable form.
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP 03/50374

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 6, 15

because:

☒ the said international application, or the said claims Nos. 15 (industrial applicability) relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 6

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the Standard.

☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

| | | |
|-------------------------------|-------------|-------------|
| Novelty (N) | Yes: Claims | 1-5,7-16 |
| | No: Claims | |
| Inventive step (IS) | Yes: Claims | 1-5,7-16 |
| | No: Claims | |
| Industrial applicability (IA) | Yes: Claims | 1-5,7-14,16 |
| | No: Claims | |

2. Citations and explanations

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP 03/50374

Section III:

1. Claim 15 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (Article 34(4)(a)(I) PCT).
2. Claim 6, essentially, relates to a prodrug of the present compounds (I). Since the claim does not state the technical features which would characterise the compound in terms of possible structures, the claim is considered to embrace compounds of hypothetical and unknown structure. Thus, the claim lacks clarity to such an extent that a meaningful search was not possible, and consequently, no opinion will be formulated for the subject-matter of this claim (Rule 66.1 (e) PCT).

Section V:

1. The invention relates basically to tricyclic isoxazolines with anti-depressant activity. The relevant prior art as defined by the PCT is given by the following documents.

D1: WO-A-97 25317

D2: WO-A-95 07893

D3: EP-A-0 885 883

D4: EICHINGER K ET AL: 'A CONVENIENT SYNTHESIS OF 3- AND 3,4-SUBSTITUTED 4,5-DIHYDROISOXAZOLE-5-ACETIC ACIDS' SYNTHETIC COMMUNICATIONS, MARCEL DEKKER, INC., BASEL, CH, vol. 27, no. 16, 1997, pages 2733-2742, XP001006906 ISSN: 0039-7911

The products disclosed in D1, D2 and D3 do not have the partially saturated isoxazole ring of the present compounds. The product 4b of D4 does not exhibit the present piperidine or piperazine ring "Pir" of the formula (I). Accordingly, the claimed matter appears to meet the requirements of Art. 33(2) PCT.

2. D1 (or D2) is considered to represent the closest prior art, because the compounds disclosed therein share the pharmacological utility with the present antidepressive and CNS active agents. The prior art does not have the alkylene space between the tricycle and the piperidine/piperazine ring. Moreover, the prior art tricycle exhibits an aromatic oxazole ring instead of the present dihydro variant thereof. It appears that there is no incentive to make these structural modifications

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP 03/50374

derivable from the closest prior art, since the said differences relate essentially to unmodifiable fragments in D1 (or D2). That is to say, the skilled person would not have no motivation to perform the indicated modification, he was also not guided by a general structure-activity principle. Accordingly, the claimed matter, which solves the problem of providing further antidepressive and CNS active agents, appears to meet the criteria of Art. 33(3) PCT.